In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

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BO DEPENA and NATALIE DEPENA, legal representatives of a minor child, RHONE DEPENA,	*	No. 13-675V
	*	Special Master Christian J. Moran
Petitioners,	*	Filed: February 22, 2017
v.	*	Entitlement, MMR vaccine, pneumococcal pneumonia, animal models
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	
* *		

Michael Baseluos, Baseluos Law Firm, San Antonio, TX, for petitioners; Heather L. Pearlman, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Rhone DePena, the son of the petitioners Bo and Natalie DePena, received a dose of the measles-mumps-rubella (MMR) vaccine when he was seven years old. Within a few weeks, he developed a severe pneumonia for which he was hospitalized for many weeks. During this time, the treating doctors determined that a bacteria, known as pneumococcus, infected his lungs and caused the pneumonia.

The DePenas claim that the MMR vaccine caused Rhone's pneumonia. Through an expert with a background in pediatric pulmonology, Boris Lokshin, they allege that the MMR vaccine weakened a portion of Rhone's immune system

[1] The E-Government Act, 44 § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services), requires that the Court post this decision on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

and, in his debilitated state, Rhone could not resist the pneumococcus infection. The Secretary has disagreed with this argument and presented the views of an expert with a background in pediatric immunology, Neil D. Romberg. In Dr. Romberg's view, the MMR vaccine does not affect the part of a human being's immune system that responds to pneumococcus infections.

Between the two experts, the Secretary's expert was more persuasive. First, Dr. Romberg has a stronger background in the relevant field, immunology. Second, the Secretary established that his expert's opinions are grounded in immunologic principles that have been established and accepted for decades. Indeed, even Dr. Lokshin did not seriously contest much of Dr. Romberg's opinion. Third, to the extent that Dr. Lokshin presented an innovative theory based on relatively recent mouse models, the Secretary effectively rebutted that evidence by showing that mice do not model what happens to human beings facing a pneumococcal infection. For these reasons, the DePenas have failed to meet their burden of proof.

Procedural History

The course of litigation has been relatively routine. The DePenas filed the petition on September 12, 2013. Within approximately two months, they submitted Rhone's medical records.

On May 28, 2014, the Secretary submitted his report, filed pursuant to Vaccine Rule 4. After a review of the medical records, the Secretary recommended that compensation be denied because the DePenas had not presented any evidence in the form of a medical record from a treating doctor or a medical opinion to demonstrate that a vaccine caused Rhone's pneumonia. Resp't's Rep. at 11.

The DePenas retained Dr. Lokshin. As mentioned previously, Dr. Lokshin's specialty is pediatric pulmonology. Exhibit 19 (curriculum vitae). Before the hearing, they submitted four reports from him. Exhibits 21 (Feb. 28, 2015), 22 (May 31, 2015),[2] 23 (Aug. 5, 2015), and 25 (Dec. 15, 2015). The literature on which Dr. Lokshin relied was appended to his reports as numbered tabs. The undersigned has reviewed all these articles.

In response to Dr. Lokshin, the Secretary retained Dr. Romberg, a pediatric immunologist. See exhibit B (curriculum vitae). Dr. Romberg authored three

[2] Dr. Lokshin's May 31, 2015 report largely, but not entirely, repeats the material in the February 28, 2015 report.

reports: exhibits A (May 5, 2015), P (June 30, 2015), and FF (Jan. 27, 2016). The Secretary filed the literature on which Dr. Romberg relied as separate exhibits marked with consecutively assigned letters. The undersigned has reviewed all these articles as well.

After unsuccessful efforts to resolve the case informally, it was set for a hearing. Before the hearing, the parties submitted briefs, which narrowed the issues. For example, the Secretary conceded that the Rhone developed pneumonia within a time after vaccination for which it is appropriate to infer causation. Resp't's Preh'g Br., filed Jan. 27, 2016, at 23.

A hearing was held in San Antonio, Texas on February 11, 2016. Both Mr. and Ms. DePena testified about Rhone's health before and after the September 15, 2010 MMR vaccination. The DePenas also called Dr. Lokshin. The Secretary's witness was Dr. Romberg. For various reasons, the hearing did not proceed as expeditiously as anticipated, and the hearing did not conclude despite continuing until the early evening.

After the first session of the hearing ended, the DePenas submitted additional information responding to issues that arose during the February 11, 2016 hearing. Another hearing was held on April 12, 2016, during which the attorneys and the witnesses appeared by videoconferencing.

Following the hearing, the parties made additional submissions. The DePenas filed another report from Dr. Lokshin. Exhibit 30.[3] The Secretary filed one brief. With the submission of the DePenas's reply brief and another report from Dr. Lokshin, the case is ready for adjudication.

Facts

The parties' disagreement in this case concerns whether Rhone's MMR vaccination weakened a relevant portion of his immune system, making him more susceptible to pneumococcus. The facts outlined below which underlie that disagreement, however, are largely undisputed. This section outlines Rhone's early health, the operation of pneumococcus, the general operation of the MMR vaccine, Rhone's health following the MMR vaccination, and the overall operation

[3] Filing an unrequested expert report was a mistake. Rather than filing more evidence, the DePenas should have filed a brief in which they marshalled the already admitted evidence in support of their claim. Nevertheless, the DePenas's recent submissions, including the attached medical articles, have been considered.

of the immune system. These facts are the foundation for the subsequent evidentiary analysis.

1. Rhone's Early Health

Rhone was born in 2003. Exhibit 9 ¶ 1. Until he was seven years old, Rhone's health was normal. See exhibit 5 (records from Northeast Pediatric Associates) passim. He participated in typical activities such as swimming, biking, playing tennis, and playing basketball. Exhibit 9 ¶ 2; Tr. 16, 54.

In his periodic visits to his pediatrician, Rhone received vaccinations, although not on the typically recommended schedule. See exhibit 1. In August 2004, Rhone received the first dose of the MMR vaccine. Exhibit 1 at 1.[4] On November 11, 2003, March 30, 2004, and June 22, 2005, Rhone received doses of the pneumococcal conjugate vaccine. Exhibit 1 at 1.[5]

2. Pneumococcus[6]

Pneumococcus is a type of bacterium. Dorland's Illustrated Medical Dictionary 1470, 1782-83 (32d ed. 2012). There are more than 90 strains of pneumococcus and the numerous strains contribute to the difficulty in developing an effective vaccine. Exhibit 21.10 (Test ID: PN23 *Streptococcus pneumoniae* IgG Antibodies, 23 Serotypes, Serum, Mayo Clinic (undated), http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/83640); see also Tr. 274, 331. The outside capsule of pneumococcus is comprised of polysaccharides. Tr. 231. Polysaccharides are carbohydrates, like sugars. Tr. 268; Dorland's at 1493

[4] Early in the litigation, the DePenas contended that Rhone broke out in an extensive rash shortly after receiving MMR at age two. Exhibit 8 (statement from Ms. DePena) at 1; see also exhibit 6 at 9-11 (record from Dr. Infante, dated April 13, 2011); Suppl. Pet. No. 1, filed Nov. 11, 2013 ¶ 6. However, the evidence showed that Ms. DePena's recollection was incorrect. While Rhone did have a widespread rash in September 2005, see Tr. 40-41, exhibit 11, this rash occurred more than one year after the first MMR vaccination. Tr. 38.

[5] The pneumococcal conjugate vaccine is often referred to by its brand name: Prevnar. The pneumococcal conjugate vaccine given to Rhone between 2003 and 2005 protected against seven strains of the pneumococcal bacteria. Exhibit 21.11 (Pneumococcal Vaccination: Who Needs It?, Centers for Disease Control and Prevention (Jan. 25, 2015), http://www.cdc.gov/vaccines/vpd-vac/pneumo/vacc-in-short.htm.

[6] A more formal name for pneumococcus is streptococcus pneumoniae. Tr. 268. For consistency, this decision uses the term "pneumococcus."

(defining polysaccharide). When faced with a polysaccharide invader, the body's adaptive immune system responds by producing antibodies, which come from B cells, and the body does not produce T cells in response. Tr. 216-17. Consequently, pneumococcus has been categorized as a type II T cell-independent antigen. Tr. 217.

The body's encounter with pneumococcus is unusual in the sense that the first step is colonization. Tr. 110. Colonization means that a strain of pneumococcus is living in a person's nose and throat. Tr. 186; cf. Dorland's at 387. This nasopharyngeal colonization is extremely common with estimates exceeding 25 percent. Exhibit S (Jeremy S. Brown et al., The classical pathway is the dominant complement pathway required for innate immunity to *Streptococcus pneumoniae* infection in mice, 99(26) Proc. of Nat'l Acad. of Sci. of the U.S. 16969 (2002)) at 16969; exhibit 23, tab 4 (Jeffrey Pido-Lopez et al., Acquisition of Pneumococci Specific Effector and Regulatory Cd4+ T Cells Localising within Human Upper Respiratory-Tract Mucosal Lymphoid Tissue, 7(12) PLoS Pathogens e1002396 (2011)) at e1002396; exhibit 25, tab 2 (R Wilson et al., Protection against *Streptococcus pneumoniae* lung infection after nasopharyngeal colonization requires both humoral and cellular immune responses, 8(3) Mucosal Immunology 627 (2015)) at 628 ("almost universal"); Tr. 144 (Dr. Lokshin: pneumococcus is so common, "we cannot really avoid it"); see also Tr. 122 (Dr. Lokshin reading from Wilson article). Colonization, which is also known as carriage, is especially frequent in the very young and the very old. Tr. 272, 329-30.

During colonization of the mucosal surfaces of the nose and throat, the body's adaptive immune system produces an antibody known as immunoglobulin A. Tr. 344; exhibit 25, tab 12 (Jason W. Rosch et al., A live-attenuated pneumococcal vaccine elicits CD4 T-cell dependent class switching and provides serotype independent protection against acute otitis media, 6(1) EMBO Molecular Med. 141 (2013)) at 142; see also Dorland's at 919-20 (immunoglobulin secretory i. A). On some occasions, and in some people, a colonization resolves without a worsening of symptoms. Tr. 219-20; Resp't's Posth'g Br., filed July 27, 2016, at 2 (citing exhibit OO (Barry M. Gray et al., Epidemiologic Studies of *Streptococcus pneumoniae* in Infants: Acquisition, Carriage, and Infection during the First 24 Months of Life, 142(6) J. Infect. Dis. 923 (1980)) at 928, fig. 5).

However, pneumococcus can also migrate from the nasopharynx to other portions of the body. Although the petitioners describe the T cells' role in the change from colonization to infection as a "critical" issue in this case (Pet'rs' Preh'g Br., filed Dec. 15, 2015, at 8), relatively little is known about how this

change occurs. See Tr. 111, 343. When pneumococcus moves to the ears and sinuses, it causes otitis media and sinusitis. Tr. 237-38, 270; exhibit OO. These types of infections are both relatively common and mild. Tr. 202-03. It is much more alarming when pneumococcus infects the lungs, causing a condition called pneumococcal pneumoniae. Dorland's at 1474.

In the United States in 2015, more than one million people suffered from pneumococcal pneumoniae. Tr. 270 (Dr. Romberg); see exhibit 21.10 (Mayo Clinic); see also exhibit 25, tab11 (Marianne W. Mureithi et al., T Cell Memory Response to Pneumococcal Protein Antigens in an Area of High Pneumococcal Carriage and Disease, 200 J. Infect. Dis. 783 (2009)).

As previously mentioned, the body's response to a pneumococcal infection is to produce antibodies. For more than 100 years, scientists have believed that antibodies (not T cells) are the way the adaptive immune system responds to pneumococcus. Exhibit 23, tab 4 (Pido-Lopez); Tr. 439, 506.[7]

According to Dr. Lokshin, it is likely that Rhone had pneumococcus in his nasopharynx before receiving the MMR vaccination. Tr. 203.

3. MMR Vaccination

At an appointment with his pediatrician, Frederick Rhame, on September 15, 2010, Rhone received a series of vaccinations. Exhibit 1; exhibit 5 at 6, 15. For this case, the relevant vaccine is the measles-mumps-rubella vaccine.

The MMR vaccine is an attenuated vaccine, that is, the vaccine contains a weakened form of the live measles virus. In its wild (or natural) state, the measles virus is extremely virulent. Measles causes the death of thousands of unvaccinated people each year.

The people who survive measles infection are more vulnerable to infection from other pathogens for 1-4 weeks. Scientists have recently theorized that the measles virus destroys the memory aspect of the survivor's immune system. Without this memory in their immune system, survivors of the measles virus may be unable to fight off infection and may contract diseases. Exhibit Y (Michael J. Mina et al., Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality, 348(6235) Science 694 (2015)) at 694.

[7] As discussed more extensively below, the petitioners, by contrast, are advancing a theory in which the body's response to pneumococcus requires T cells.

Dr. Romberg, the Secretary's expert, conceded that the MMR vaccine can have the same consequence as the wild measles virus: a suppression of some parts of the adaptive immune system. Dr. Romberg's concession on this point simplified the litigation.[8]

4. Rhone's Medical History Immediately Following MMR Vaccination (September 2010 through October 2010)

As just stated, when he was vaccinated, Rhone encountered a weakened form of the measles virus on September 15, 2010. Two days later, Rhone's mother called to report that he had a "bad reaction to shots" and requested a "steroid cream." Exhibit 5 at 31; see also Tr. 17. Although the nurse's note does not verbally describe the nature of the reaction, the pediatrician's record includes a photograph showing raised dots on his thigh. Exhibit 5 at 38; see also exhibit 11; Tr. 17, 41, 56, 264, 372.

On Saturday, September 25, 2010, Rhone's parents brought him to the emergency room at Methodist Children's Hospital because he was having lower back pain. Rhone also had been coughing for two days and his temperature, according to his mother, was "high for him." Exhibit 7 at 32; exhibit 8 at 1. The doctors diagnosed him as having an acute viral syndrome. Exhibit 7 at 35; see also Tr. 21.

Rhone's health did not improve over the next few days. On Tuesday, September 28, 2010, Rhone's mother took him to Dr. Rhame's office because of a high fever, greyish color, and grunting sounds when he was breathing. Tr. 22. Dr. Rhame sent him for testing, including a chest X-ray. Exhibit 5 at 46; exhibit 8 at 1. The chest X-ray showed bilateral pneumonia. Exhibit 5 at 46.

Rhone's pneumonia was severe. He remained at Methodist Children's Hospital for 21 days. Exhibit 7 at 62. His mother described the frightening details in her statement, although the course of how the doctors treated Rhone is not

[8] In addition to the Mina article (exhibit Y), other articles relevant to how the measles virus and the measles vaccine may suppress the immune system include exhibit 21, tab 1 (Philip Fireman et al., Effect of Measles Vaccine on Immunologic Responsiveness, 43(2) Pediatrics 264 (1968)), and exhibit 21, tab 3 (Christopher L. Karp et al., Mechanism of Suppression of Cell-Mediated Immunity by Measles Virus, 273 Science 228 (1996)).

relevant to determining whether the MMR vaccine contributed to the pneumonia. See exhibit 8 at 2-3; Tr. 23-27.

The doctors determined that Rhone was infected with pneumococcus. Exhibit 7 at 63, 91, 112, 171. There is no doubt that the pneumococcus caused Rhone's pneumonia. Tr. 203. The only question raised in this litigation is whether the MMR vaccine contributed to it.

Near the end of Rhone's hospitalization, the doctors tested Rhone's blood for the presence of titers against 14 serotypes of pneumococcus. For three strands, Rhone had levels of antibodies that exceeded 1.3 μg/mL, which is considered the threshold for protective levels. See exhibit 7 at 501 (results dated October 11, 2010); Tr. 97, 327, 334-36 (explaining protective level). One strand was 1.15 μg/mL. Rhone's titers for the remaining antibodies were less than 1.0 μg/mL. Exhibit 7 at 501.

After recovering in the hospital, Rhone was discharged on October 18, 2010. Exhibit 7 at 62-64; see also Tr. 27-28, 58.

5. Medical History after October 2010

Rhone's pulmonologist, Amanda M. Dove, followed his case for several months. Exhibit 3 at 8-17. In June 2013, Dr. Dove assessed Rhone as having mild reactive airway disease. Exhibit 3 at 2. She prescribes medication for an inhaler. Tr. 46.

In August 2015, a CT scan of Rhone's chest was normal, except for some slight scarring. Exhibit 24 at 1. A spirometry test was also normal. Id. at 6; see also Tr. 193.

Prompted by questions that arose in this litigation, the DePenas obtained additional information about Rhone's antibody levels in 2016. This testing indicated that Rhone's antibody levels were low to 13 serotypes of pneumococcus. Exhibit 27; Tr. 455, 489.

At the time of the first hearing, Rhone had improved. He sometimes had problems breathing and ran slower than his peers. Tr. 35-35, 60. The DePenas emphasize that after Rhone's 2010 pneumonia, which followed the MMR vaccination, Rhone has not had another episode of pneumonia. Tr. 34, 59, 168.

6. Operation of the Immune System

A body's responses to foreign invaders, often called antigens or pathogens, are controlled by the immune system. See Dorland's at 1861. Immunologists generally divide the immune system into two branches: the innate immune system and the adaptive immune system. Tr. 266.

Innate Immune System. The innate immune system is relatively primitive. The innate immune system generally recognizes foreign invaders. Tr. 266. Components of the innate immune system include cytokines, natural killer cells, and complement. Tr. 214, 225-26.

According to Dr. Romberg, the innate immune system contributes to how the body responds when pneumococcus becomes infectious. Exhibit P (Dr. Romberg report) at 3 (citing exhibit S (Brown), exhibit T (Carolyn Mold et al., Protection from *Streptococcus pneumoniae* Infection by C-Reactive Protein and Natural Antibody Requires Complement But Not Fcγ Receptors, 168 J. of Immunology 6375 (2002))); Tr. 326-27. Dr. Lokshin stated that Dr. Romberg's report nicely described the innate immune system. Tr. 117. Dr. Lokshin also acknowledged that the "Innate immune system clearly has a very big role in killing pneumococcus. That's not in question." Tr. 467.

Adaptive Immune System. In comparison to the innate immune system, the adaptive immune system is more advanced. The adaptive immune system recognizes specific antigens. Tr. 266.

The adaptive immune system contains two types of cells: B cells and T cells. See Dorland's at 1084 (defining lymphocyte). Dr. Lokshin and Dr. Romberg appear to agree about the primacy of B cells in responding to pneumococcus.[9]

B cells. B cells make antibodies. Tr. 267. Antibodies, in turn, can be classified into different types of immunoglobulin. See Dorland's at 100. Antibodies recognize polysaccharides (or sugars). Tr. 269, 461. Antibodies' ability to respond to polysaccharides is one trait that distinguishes them from T cells.

[9] The dispute is over the role of T cells in the body's response to a pneumococcus infection.

T cells. The other part of the adaptive immune system is T cells. T cells derive their name from the thymus, where they mature. Tr. 302; Dorland's at 1925 (thymus).

T cells are further classified. The basic division is into two groups, known as cytotoxic T cells and helper T cells. Cytotoxic T cells, which are also known as CD8+ cells, kill cells that are infected by viruses. Tr. 267, 358. For example, when the body is infected by cytomegalovirus ("CMV"), cytotoxic T cells respond. Tr. 435.[10]

There are multiple types of helper T cells, also known as CD4+ cells. Th1 cells help cytotoxic T cells kill cells infected with infectious agents, especially viruses.[11] Tr. 267, 296. Th2 cells help B cells. Tr. 268, 297. Th17 cells help cells at the mucosal level respond to infections by generating interleukin ("IL") 17.[12] 354. Another type of helper T cell makes sure that the immune system does not overrespond. These helper T cells are known as T regulatory cells. Tr. 137, 268. Adopting a simile that Dr. Lokshin proposed, Dr. Romberg described helper T cells as the conductor of an orchestra in that they help other cells do their job. Tr. 267; see also Tr. 102-04.

The crux of the disagreement between Dr. Lokshin and Dr. Romberg concerns whether T cells contribute to the body's response to a pneumococcal infection. Dr. Lokshin opines that T cells have a role in the immune system's response. In contrast, Dr. Romberg opines that T cells are expendable. The following sections are reasons why Dr. Romberg's opinion is more persuasive.

Standards for Adjudication

In the analysis section below, evidence in this case will be analyzed according to the following standards of adjudication.

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[10] In this context, Dr. Romberg was asked hypothetically, if a person developed a CMV infection within three weeks of an MMR vaccination, could the suppression of the immune system by MMR contribute to the CMV infection? Dr. Romberg responded that this "mechanism makes biologic sense." Tr. 436. Dr. Romberg's willingness to recognize the potential adverse consequences to vaccination enhanced his credibility.

[11] Without contradiction, Dr. Romberg stated that the measles vaccine can suppress Th1 cells, not Th2 cells. Tr. 421.

[12] Interleukins are types of cytokines. Dorland's at 949. Cytokines, in turn, are proteins by which cells of the immune system communicate. Id. at 466.

Petitioners are required to establish their case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

Special masters are fact finders that use their accumulated expertise to judge the individual merits of claims. See Hodges, 9 F.3d at 961; Munn v. Sec'y of Health & Human Servs., 970 F.2d 863, 871(Fed. Cir. 1992). Thus, the probative value of the evidence, the credibility of the witnesses, and the relative persuasiveness of the competing medical theories of the case, are within their purview. Moberly, 592 F.3d at 1326 ("Finders of fact are entitled-indeed, expected-to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Lampe, 219 F.3d at 1361-62. Special masters may use the Daubert framework for analyzing the admissibility of scientific, technical, or other specialized knowledge, and the rules of evidence require the testimony to have a reliable basis in the relevant discipline. Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999).

The elements of the DePenas' case are set forth in the often cited passage from the Federal Circuit's decision in Althen: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Analysis

To analyze the petitioners' T cell-centered immunology theory requires both an understanding of both the parties' experts' qualifications and basic principles of immunology. The analysis below first focuses on the experts' qualifications, and second reviews widely accepted principles of immunology related to pneumococcal infection. With the experts' qualifications and the basic principles of immunology as foundations, the analysis goes on to assess the reliability of the petitioners' new immunologic theory.

1. Expert Qualifications

In considering the value of opinion testimony, special masters may consider the offeror's expertise. See Snyder v. Sec'y of Health & Human Servs., 553 F. App'x 994, 1000–02 (Fed. Cir. 2014) (special master's finding that respondent's experts were more persuasive due in part to their current practice in neurology compared to petitioner's expert who had no recent practice was not arbitrary or capricious); see also Copenhaver v. Sec'y of Health & Human Servs., 129 Fed. Cl. 176, 183 (2016) (rejecting argument that special master erred in evaluating the qualifications of the experts); Tompkins v. Sec'y of Health & Human Servs., 117 Fed. Cl. 713, 719 (2014) (noting special master reasonably articulated one expert's relative lack of training and experience as a basis for not crediting the witness); Holmes v. Sec'y of Health & Human Servs., 115 Fed. Cl. 469, 490 (2014) (stating the special master was reasonable in considering a testifying expert's "research credentials in the field"); Locane v. Sec'y of Health & Human Servs., 99 Fed. Cl. 715, 727 (2011) (finding special master rationally credited an expert with specialization in the disease in determining when the petitioner's disease began), aff'd, 685 F.3d 1375, 1380 (Fed. Cir. 2012).

Here, the primary question is how the body responds to pneumococcal colonization or infection. This question is about human immunology. Therefore, the qualifications of the experts are reviewed with an emphasis on immunology.

A. Dr. Lokshin

Dr. Lokshin graduated from medical school and completed a pediatric internship in Russia. He completed a second pediatric internship in California, where he also had a pathology residency and a pediatric residency. Exhibit 19 (curriculum vitae).

From 1988-90, Dr. Lokshin had a joint fellowship in allergy / immunology and pediatric pulmonology at the University of Iowa. In describing his expertise in immunology, Dr. Lokshin emphasized this stage of his medical career. Tr. 64.

After his Iowa fellowship ended, Dr. Lokshin completed another residency in pediatrics and then completed another fellowship, this time in pediatric pulmonology. Both of these fellowships were through the University of Missouri-Columbia School of Medicine, where he also served as an assistant professor in pediatric pulmonology from 1991 through 1993. Exhibit 19. In 1993, the most recent of five articles written by Dr. Lokshin was published. Id.; see also Tr. 72.

Dr. Lokshin's next teaching position was in Connecticut at the Yale-New Haven School of Medicine. During this time (1993-95), he also served in the pediatric pulmonology / allergy division within the department of pediatrics at Danbury Hospital. He first became board certified in pediatric pulmonology in 1996, when he was living in Nevada. Exhibit 19; see also Tr. 62.

For some time after May 1996, Dr. Lokshin taught allergy to medical students in large lecture classes at the University of Nevada, Reno. Exhibit 19; Tr. 73. Dr. Lokshin's current teaching involves working with a single student for a few weeks in his office. Tr. 74. His current employment, which started in 1995, is working in a practice consisting of two doctors, called Allergy and Asthma Associates. Exhibit 19; Tr. 63. He usually sees one patient or two patients with pneumococcal pneumonia each year. Tr. 70.

After the petitioners offered Dr. Lokshin as an expert in the relationship between "T cells and invasive pneumococcal disease," the Secretary objected. Tr. 68. The ensuing voir dire brought out that Dr. Lokshin is not board certified in immunology. He has not received any special training on T cells. Tr. 73. He was not performing any research. Tr. 72. His work in treating patients with allergies draws upon his knowledge of immunology because allergy is a subtype of immunology. Tr. 75-79.

Ultimately, he was recognized as an expert in pediatric pulmonology. He possesses the minimum qualifications to testify about immunologic concepts because of his training and experience. However, his testimony on immunologic topics was presented with the risk of being given less weight because of his relative lack of experience in immunology. Tr. 80-81.

Dr. Lokshin's lack of specialized training in immunology affected the quality of his testimony. When Dr. Lokshin presented the articles on which he

relied, he frequently stated that he was not presenting his opinion, he was simply presenting a view someone else expressed. Tr. 77, 84, 85, 100, 130, 213. While it is hornbook law that a testifying expert may rely upon the work of another expert if the testifying expert would normally rely upon the second expert's work, see Summit 6, LLC v. Samsung Electronics Co., Ltd., 802 F.3d 1283, 1299 (Fed. Cir. 2015), Dr. Lokshin often left the impression that he did not have the depth of experience in immunology necessary to evaluate and render an opinion on immunologic topics.

For example, when asked to explain the components of the innate immune system, Dr. Lokshin provided a brief answer, but added that if more information were needed, he would need to research the topic separately. Tr. 214. As another example, Dr. Lokshin used terminology about the immune system that was at least unusual, and possibly incorrect.[13] He talked about the "three pillars of the immune system," referring to the innate immune system, B cells, and T cells. Tr. 115. Traditionally, however, immunologists divide the immune system into the innate immune system and the adaptive immune system. See Tr. 266. The adaptive immune system is further divided into B cells and T cells.[14] Id.

Similarly, Dr. Lokshin's presentation of articles was extremely cursory. Despite the undersigned's recommendation that the petitioners and Dr. Lokshin discuss a smaller number of articles with a deep level of analysis, petitioners and Dr. Lokshin more often skimmed the surface of many articles. The petitioners and Dr. Lokshin would have been better served to focus on fewer articles but discuss their complicated immunology more thoroughly. Although the undersigned has reviewed all the articles, more in depth testimony from Dr. Lokshin about the significance of the articles could have promoted the petitioners' case.

The intent of these examples is not to catch Dr. Lokshin in small errors, but explain why he did not appear fluent in the language of immunology. This lack of fluency, again, gave the impression that Dr. Lokshin had limited experience on

[13] Similarly, the petitioners' briefs sometimes contain phrasing that lacks precision. For example, petitioners asserted "The immune systems contains two (2) lines of defenses: T cell lymphocytes (cell mediated immunity) and B cell dependent specific antibodies (humoral immunity)." Pet'rs' Preh'g Br. at 5. This statement overlooks the innate immune system. The petitioners also asserted that "CD4 is a synonym for T cells." Id. at 9 n.9. Actually, CD4 cells are a type of T cells. Tr. 358. As explained above, some T cells are not CD4 cells.

[14] The way Dr. Lokshin described the immune system is akin to saying that the federal government of the United States is divided into four components: the Executive Branch, the Judicial Branch, the Senate, and the House of Representatives.

which to base his opinions. This impression, in turn, diminished the overall value of Dr. Lokshin's testimony. See Snyder, 553 F. App'x at 1000–02 (noting the special master did not find persuasive the testimony of expert who read literature to support his opinion but did not actually treat patients with the relevant disease); Daubert v. Merrell Dow Pharm., Inc., 43 F.3d 1311, 1317 (9th Cir. 1995) ("[o]ne very significant fact to consider is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying").

B. Dr. Romberg

Dr. Romberg graduated from Pennsylvania State College of Medicine in 2004. He was a resident in pediatrics at New York University School of Medicine from 2004 to 2008, with the last year as pediatric chief resident. He completed a fellowship in allergy and clinical immunology at Yale University from 2008-11. Tr. 257-59; exhibit GG.[15]

In 2011, Dr. Romberg began his teaching career at Yale. He remained at Yale with various titles and responsibilities until 2015. During this time, he obtained his board certification in allergy and immunology. He also wrote at least six papers about immunology, which were published in peer reviewed journals. Some of the papers focus on B cells. Exhibit GG at 3-5. Through grants, the National Institute of Health funded his research on human immunology. Tr. 259.

In 2015, he was appointed to the Jeffrey Modell Chair of Pediatric Immunology Research at Children's Hospital of Philadelphia. Dr. Romberg explained that this position gives him indefinite funding for his research on deficiencies in the immune system. Tr. 260.

Although Dr. Romberg's primary vocation is research, Tr. 259, he also treats children whose immune systems are missing parts. Tr. 275. He estimated that he has treated 40-60 patients with pneumonia, although he did not specify whether the patients with pneumonia also had defective immune systems and did not specify whether pneumococcus caused the pneumonia. Tr. 401.

Overall, Dr. Romberg's knowledge about immunology was impressive. His demeanor and the content of this testimony demonstrated that he understood how the human immune system functions to a level of great detail. He took care to be

[15] Exhibit GG is an updated version of Dr. Romberg's curriculum vitae. The previous curriculum vitae was filed as exhibit B.

precise in his wording. See Tr. 358. On immunologic topics, Dr. Romberg was, simply, a much stronger witness than Dr. Lokshin. See Moberly, 592 F.3d at 1326 (recognizing that special masters are obligated to evaluate the evidence, including the experts, before them).[16]

2. Principles of Immunology Related to Pneumococcal Infection

Because the petitioners maintain that the MMR vaccine impaired Rhone's ability to create T cells and the ensuing lack of T cells created a vulnerability to a pneumococcal infection, their case depends on T cells preventing a pneumococcal infection in a human being. As expert testimony unfolded, there was little dispute about the principles underlying the immune system's response to pneumococcal infection. Dr. Lokshin agreed with Dr. Romberg about multiple things that undermine a primary role for T cells in fighting pneumococcal infection.

As outlined below, both Dr. Lokshin and Dr. Romberg agreed that an effective response to pneumococcal infection requires both the innate immune system and antibodies from the adaptive immune system. Additionally, Dr. Lokshin did not dispute that T cells do not respond directly to pneumococcal infection (most likely because the external surface of pneumococcus is primarily composed of polysaccharides). Further, Dr. Lokshin did not dispute Dr. Romberg's observations regarding humans suffering from X-linked agammaglobulinemia and severe combined immune deficiency (SCID), which strongly support the argument that T cells are expendable in the body's response to pneumococcal infection. In short, the following concessions by Dr. Lokshin undermine his ability to maintain that T cells have a significant role in fighting pneumococcal infection in human beings.

[16] As mentioned earlier, the theory that the DePenas and Dr. Lokshin advanced involved immunology. Therefore, the qualifications of the respective experts in immunology are paramount. In saying that Dr. Lokshin was not as persuasive on immunology, the undersigned does not intend to denigrate Dr. Lokshin's qualifications as a pediatric pulmonologist.

A. An Effective Response to Pneumococcal Infection requires both the Innate Immune System and Antibodies from the Adaptive Immune System

Throughout this litigation, Dr. Romberg has maintained that in response to pneumococcal infections, T cells are expendable. In his first report, Dr. Romberg wrote:

> It has been known for more than 6 decades that serum soluble factors like complement components, C-reactive protein and immunoglobulins form the basis of human immunity to *Streptococcus Pneumonia*. These serum proteins target the capsular polysaccharide residues that cover pneumococcus and it is the presence of pneumo[co]ccal-specific IgG antibodies especially which confer meaningful protection to blood borne and lung infections.

Exhibit A at 3. He continued this position in a subsequent report and in his testimony. Exhibit P at 3; Tr. 273, 418, 439-40.

On the other hand, Dr. Lokshin's reports and testimony focused on the role of T cells. E.g., Tr. 215, 485. He attempted to explain that T cells are a part of the body's response to a pneumococcal infection. Near the end of the second hearing day, Dr. Lokshin presented his views on the value of antibodies. He stated: antibodies "are highly effective. I don't think anybody disagree[s] with that, and that's a pretty old finding that is well established, and there is absolutely no disagreement about that." Tr. 460.

Later still in his testimony, Dr. Lokshin also agreed that the innate immune system also "has [a] very big role in killing pneumococcus. That's not in question." Tr. 467.

With these two passages, Dr. Lokshin has essentially agreed with Dr. Romberg that an effective response to a pneumococcal infection can come from the innate immune system and antibodies. The only remaining question is whether T cells contribute to this response.

B. T Cells Do Not Respond Directly to a Pneumococcal Infection

On a very simple level, antibodies respond to polysaccharides, and T cells respond to proteins. The capsule of pneumococcus is (mostly) comprised of

polysaccharides. See Tr. 216-17 (Dr. Lokshin). Therefore, antibodies (and not T cells) respond to pneumococcus.

Although the connection between antibodies and polysaccharides and the lack of connection between T cells and polysaccharides was generally not disputed, Dr. Romberg explained some of the highly technical experiments underlying these postulates. For example, he discussed an article reporting on competitive affinity experiments that demonstrated that T cells cannot see polysaccharides.[17] Tr. 299-302, 421-24 (both discussing exhibit W (Clifford V. Harding et al., Effects of pH and polysaccharides on peptide binding to class II major histocompatibility complex molecules, 88 Proc. of Nat'l Acad. of Sci. of the United States of America 2740 (1991))). According to the abstract, the Harding article shows "T-cell independence of polysaccharide antigens." Exhibit W at 2740.

T cell independence was another way in which the disagreement between Dr. Lokshin and Dr. Romberg was manifest, particularly in regard to exhibit X (James J. Mond et al., T Cell-Independent Antigens Type 2, 13 Annual Review Immunology 655 (1995)). Dr. Lokshin quoted a portion of this article that states: "All of these studies demonstrated that responses to TI [T cell independent] antigens could be T cell regulated and/or T cell dependent, despite their inability to stimulate MHC class II-dependent T cell help; thus their classification as T cell-independent is not entirely accurate." Tr. 147 (quoting exhibit X at 663). From this basis, Dr. Lokshin asserted that T cell independence is a relative term. Tr. 149-50. When asked about this passage, Dr. Romberg stated that T cells can help B cells make antibodies but producing antibodies that depend on T cells takes four to six weeks. Tr. 306; Cf. Tr. 419 (Dr. Romberg stating that he had not reviewed the underlying studies and, therefore, he could not comment on this portion of the Mond article).

On the other hand, the same Mond article also discussed pneumococcus specifically. Mond stated: "Early studies with Pneumococcus and other encapsulated and nonencapsulated organisms established the T cell-independence of the antibody response to the polysaccharide component." Exhibit X at 679. After citing Mond and Harding in his second expert report, Dr. Romberg asserted: "Carbohydrate antigens like those on pneumococcus belong to the category named type II T-cell independent antigens." Exhibit P at 3. When asked in the first hearing about Dr. Romberg's classifying pneumococcus as a T cell independent

[17] More technically, for a T cell to respond to a foreign invader, an antigen presenting cell must interact with the invader. Tr. 525; see also Tr. 422-23.

antigen, Dr. Lokshin agreed. Tr. 217-18. Dr. Lokshin's admission that pneumococcus is a T cell independent antigen undermines much of his opinion.[18]

Prior to the second hearing, however, petitioners submitted additional exhibits to further support the possibility that T cells can respond directly to pneumococcus. See Tr. 466; exhibits 25, tab 7 (Qibo Zhang et al., Low CD4 T Cell Immunity to Pneumolysin Is Associated with Nasopharyngeal Carriage of Pneumococci in Children, 195 J. Infect. Dis. 1194 (2007)); exhibit 25, tab 10 (Adam K. A. Wright, Experimental Human Pneumococcal Carriage Augments IL-17A-dependent T-cell Defence of the Lung, 9(3) PLOS Pathogens 1 (2013)); exhibit 25, tab 11 (Mureithi); Pet'rs' Posth'g Br. Reply, filed Aug. 26, 2016, at 1-4 (discussing the exhibits submitted between the first and second hearing). In support of a direct T cell response, petitioners argued T cells can respond to proteins, and that many capsular proteins have been isolated on the pneumococcal capsule, thus allowing T cells to see the pneumococcal capsule and respond. Tr. 441-42, 461. This argument, however, led to a nuanced discussion of how T cells function, a discussion which further highlighted Dr. Romberg's more thorough understanding of the human immune system when compared to Dr. Lokshin. Dr. Romberg did not dispute the presence of proteins outside the pneumococcal capsule, but did draw on important distinctions that undermined petitioners' response theory. See Tr. 443. He noted that the proteins outside of the pneumococcal capsule are not part of the capsule, that although proteins may be present they are not necessarily targetable by the immune system, and that T cells cannot see proteins directly, but only interact with them through an antigen-presenting cell. See Tr. 443, 524-525.

Despite the additional articles providing some evidence to the contrary, Dr. Lokshin conceded that T cells do not respond directly to pneumococcal infection. He emphasized that the T cells' alternate role in attacking pneumococcus, testifying: "It's important I think for us because it is not necessarily the T-cells themselves have [sic] to kill something. They may influence other parts of immune [sic] system that will do the job; specifically, innate [sic] immune system." Tr. 466.

[18] On redirect, the petitioners' attorney attempted to "clarify" this testimony. However, the exchange between counsel and Dr. Lokshin was confusing and did not provide a persuasive reason for rescinding Dr. Lokshin's earlier statement that pneumococcus is a T cell independent antigen. See Tr. 244-50.

C. Human Beings' Experience with Diseases is Consistent with the Distinction between T Cells and B Cells

In addition to the persuasive immunological studies cited by Dr. Romberg, his experience treating people with dysfunctional immune systems allowed him to add insights about the significance of the difference between T cells and B cells in preventing diseases. Some people do not produce B cells and they suffer from a disease known as X-linked agammaglobulinemia. Tr. 275-76. These people without B cells are vulnerable to pneumococcal infections, which they get repeatedly unless they receive antibodies. Exhibit J (Ogden C. Bruton, Agammaglobulinemia, 9 Pediatrics 722 (1952)).

Dr. Romberg interpreted the Bruton article as showing that T cells alone do not prevent pneumococcal infections. If T cells alone were effective, then the child reported in the Bruton article would not have suffered multiple pneumococcal infections. The boy's improvement after receiving antibodies is further evidence that the reason for the repeated pneumococcal infections was due to a problem in the B cells. Tr. 275-76. When asked about this article, Dr. Lokshin agreed that "If somebody gets antibodies, they will stop getting sick [with pneumococcal infections]." Tr. 505.

A different situation occurs with people suffering from severe combined immune deficiency (SCID). People with SCID lack T cells and have either no B cells or defective B cells. When untreated, they get many infections, including fungal, viral, parasitic, and pneumococcal infections. After they receive antibodies, people with SCID do not develop pneumococcal infections, although they continue to develop other types of infections. Tr. 276-77. Again, Dr. Lokshin did not disagree with Dr. Romberg on this point, although Dr. Lokshin noted that the effectiveness of antibodies in responding to pneumococcus does not provide any information about the effectiveness of T cells. Tr. 460.

3. Petitioners' New Immunology Theory Related to Pneumococcal Infection

Against this background of well-established and generally accepted precepts of immunology, Dr. Lokshin proposes a new idea. In Dr. Lokshin's opinion, a human being's response to a pneumococcal infection includes a role for T cells. Tr. 105, 114-16, 181-82.[19] To support this opinion, Dr. Lokshin initially relied upon murine (mouse) studies and later added articles based on human beings.

[19] This step links the MMR vaccine, which can rarely depress the production of T cells, to a pneumococcal infection.

Before examining the support provided by Dr. Lokshin, it bears repeating that he seems ill-equipped to topple established immunologic ideas, such as T cells do not respond to polysaccharides. Dr. Lokshin does not routinely treat patients with immunologic disorders, he does not teach classes of medical school students in immunology, he does not have any advanced certifications in immunology, and he does not currently author articles on immunology. In short, when the topic is cutting-edge immunology, Dr. Lokshin has less qualifications to present new ideas persuasively.

A. Mouse Studies

In Dr. Lokshin's initial reports, he cited several articles that reported on experiments using mice. In these tests, the researchers discovered that mice do produce T cells in response to a pneumococcal infection. At hearing, Dr. Romberg agreed that mice respond to pneumococcus infection by having a particular type of T helper cell, which is known as Th17, produce IL17. Tr. 284, 354, 516.[20] Dr. Lokshin attempted to argue that what happens in mice is what happens in human beings. Tr. 135.

The Federal Judicial Center ("FJC") has published a series of guides designed to "assist judges ... in reaching an informed and reasoned assessment concerning the basis of expert evidence." Jerome P. Kassirer & Gladys Kessler, Preface to Reference Manual on Scientific Evidence, at xv (Federal Judicial Center, 3d ed. 2011). With respect to animal studies, the FJC offered the following guidance: "The expert should review similarities and differences in the animal species in which the compound has been tested and in humans. This analysis should form the basis of the expert's opinion as to whether extrapolation from animals to humans is warranted." Bernard D. Goldstein and Mary Sue Henifin, "Reference Guide on Toxicology," in Reference Manual on Scientific Evidence (3d ed. 2011) at 661. In considering the usefulness of animal studies, a starting point is that "there is an overwhelming similarity in the biology of all living things and a particularly strong similarity among mammals." Id. at 662. However, this is not an iron-clad rule as "laboratory animals differ from humans in many ways." Id.

[20] IL 17 is an interleukin type of cytokine. See Dorland's at 949. Cytokines, in turn, are proteins by which cells of the immune system communicate. Id. at 466.

In this case, although Dr. Lokshin wanted to extrapolate from mice to humans, he did not review the similarities and differences between mice and humans. This leads to a gap in his opinion.[21]

Moreover, Dr. Romberg disagreed with Dr. Lokshin's comparison, stating that with respect to the response to pneumococcal infections, mice differ from people. Tr. 285-86; see also Tr. 120 (Dr. Lokshin: "mice are not identical to humans"), 281 (Dr. Lokshin: "Mouse immunology is not human immunology."). Literature supports this differentiation. One article stated that "mice lacking the *Il17a* and *Il17ra* genes or, to a lesser extent, the *Il17f* gene, are susceptible to a broad range of infections with bacterial and fungal pathogens at the mucosal surface. In contrast, human patients lacking a component of IL-17 immunity due to a genetic defect, have a narrower spectrum of pathogen susceptibility." Exhibit KK (Sophie Cypowyj et al., Immunity to infection in IL-17-deficient mice and humans, 42(9) Eur. J. Immunol. 2246 (2012)) at 2247; see also Tr. 286-87 (Dr. Romberg's discussion of Cypowyj).

An editorial presented a similar point, using less complex language. The authors wrote: "Translation of many other important findings from murine models to humans has been rather disappointing. This is best exemplified by models of autoimmunity and cancer immunotherapy where numerous studies showing promising outcomes in murine models have achieved limited success in a human setting." Exhibit NN (Rajiv Khanna and Scott R. Burrows, Human immunology: a case for the ascent of non-furry immunology, 89 Immunol. and Cell Biology 330 (2011)) at 330. These authors continued: "Confidence in these model systems has eroded, as we now know that there are significant differences in human physiology and the immune regulatory pathways from these animal models." Id.

This evidence has undermined the assumption that Dr. Lokshin appears to have made about the transferability of mouse studies on pneumococcus to human beings. Without some reliable showing that an extrapolation from mice to people is appropriate, the studies based upon mice are not useful.

B. Human Studies

In addition to studies on mice, Dr. Lokshin relied upon human studies to show that a person's response to a pneumococcal infection involves T cells. One

[21] Dr. Lokshin sometimes suggested that an extrapolation from mice to humans must be appropriate because otherwise scientists would not conduct experiments on mice. Tr. 135-36; 138. This suggestion is illogical and not persuasive. See Tr. 281.

person exploring this possible connection is Richard Malley, a researcher at Harvard Medical School and Boston Children's Hospital. Dr. Malley is attempting to develop a vaccine against pneumococcus that stimulates the production of T cells. One advantage to this type of vaccine is that one dose of the vaccine could lead to immunity from many (possibly all) strains of pneumococcus.

There is no doubt that some research is being done in the field. For example, petitioners submitted an excerpt showing that the National Institutes of Health has funded research into a T cell based vaccine against pneumococcus. Exhibit 25, tab 8 (Kristin Leigh Moffitt, Innate and acquired immune responses to novel pneumococcal T cell antigens, Grantome (January 27, 2017), http://grantome.com/grant/NIH/K08-AI095352-04); see also Tr. 447-48. Dr. Lokshin is "optimistic" about this research. Tr. 502.

Petitioners also submitted a press release in which a manufacturing company, Genocea, touted its progression to "phase 2" for "a novel T cell vaccine" against pneumococcal colonization. Exhibit 25, tab 9 (GEN-004 for Pneumococcus, Genocea Biosciences (Feb. 28, 2016), http://www.genocea.com/pipeline/gen004-for-pneumococcus/). Under some circumstances, this undergirding could reinforce Dr. Lokshin's opinion.

However, the company's phase 2 trials did not show any statistically significant improvement. Thus, the company suspended further development of the vaccine. Exhibit 25, tab 9 (Genocea Biosciences); see also Tr. 437-40. This failure suggests, although one failure does not absolutely prove, that the theory needs reexamination. See Daubert, 509 U.S. at 593 (recognizing whether a theory has been tested as one factor that may be considered in evaluating an expert's opinion); Terran, 195 F.3d at 1316 (endorsing a special master's use of Daubert in the Vaccine Program). Dr. Lokshin acknowledged that research into a T cell based vaccine is "just too early" and "not moving as fast as we want." Tr. 501-02; accord Tr. 472-73 (Dr. Lokshin's testimony that the Genocea article does not constitute definitive proof of the effectiveness of a pneumococcus vaccine based on T cells).

Despite the lack of success in developing a T cell based vaccine against pneumococcus, Dr. Lokshin relied upon several other articles either written with Dr. Malley or based upon his work. The goal of developing a T cell based vaccine is certainly laudatory – a successful T cell based vaccine could protect against many (maybe all) strains of pneumococcus. The potential benefits, especially in the regions of the world with less access to medical care, could be immense.

However, the worthiness of the pursuit does not automatically make any of Dr. Malley's studies a reliable basis for an expert's opinion.

As previously mentioned, Dr. Lokshin relied upon several articles from Dr. Malley or Dr. Malley's associates. The undersigned reviewed this material multiple times and has considered the testimony from both Dr. Lokshin and Dr. Romberg about those articles. [22] The articles did not present a persuasive basis for toppling the generally accepted principle in immunology that a human being's response to a pneumococcal infection does not involve T cells.

Althen Analysis

The previous section explains why Dr. Romberg's opinion was more persuasive than Dr. Lokshin's opinion. These reasons include Dr. Romberg's superior qualifications in immunology, the well accepted and well demonstrated idea that T cells cannot recognize polysaccharides, and the undeveloped effort to overturn immunologic dogma. The remaining task is to place these findings in the context of the Althen criteria.

To review, the Federal Circuit set forth the petitioner's burden regarding causation in off-Table cases as "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

1. Prong 3: Timing

The third prong of Althen requires "a showing of a proximate temporal relationship between vaccination and injury." Id. As part of their case-in-chief, the petitioners bear the burden of establishing that the onset of their child's disease

[22] Petitioners noted multiple articles showing relationships between the quantity of T cells and pneumococcal infection to support the concept that T cells influence other parts of the immune system to respond to pneumococcus. See exhibits 25 tab 7 (Zhang), 25 tab 10 (Wright), 25 tab 11 (Mureithi); see, e.g., Tr. 475 (discussing exhibit 25 tab 10). For example, Wright states that "increased rates of pneumococcal carriage in children and clinical cases of pneumonia in adults were associated with a reduction in circulating . . . T-cells." Dr. Romberg agreed that there is likely a relationship, but explained the relationship by stating that T cells probably affect pneumococcal infection by helping B cells to secrete antibodies – an idea inconsistent with petitioners' theory because it highlights the significance of B cells, vice T cells, in responding to pneumococcal, and creates a timing issue. See Tr. 306 (Dr. Romberg stating that T cells can help B cells make antibodies, however producing antibodies that depend on T cells takes four to six weeks); 446, 515.

occurred within an acceptable time. Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). This formulation implies that the third prong from Althen actually contains two parts. First, there must be a showing that a range of time is "acceptable" to infer causation. Second, there must be a showing that the vaccinee's disease arose in this acceptable time. Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542–43 (2011), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff'd per curiam, 503 F. App'x 952 (Fed. Cir. 2013).

Before the hearing, the Secretary conceded that Rhone's pneumococcal infection developed within a "medically acceptable timeframe." Resp't's Preh'g Br., filed Jan. 27, 2016, at 23. Thus, the DePenas have met their burden of proof on this prong.

However, a finding in a petitioner's favor on prong 3, by itself, does not mean that the petitioner is entitled to compensation. Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364 (Fed. Cir. 2012) (holding that the special master did not err in resolving case based upon the second prong of the Althen test); Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("Temporal association is not sufficient, however, to establish causation in fact."). The petitioners are required to establish the first and second Althen prongs, which is where their case falters.

2. Prong 1: Theory

The first prong from Althen requires the petitioners to establish "a medical theory causally connecting the vaccination and the injury." Althen, 418 F.3d at 1278. The Court of Federal Claims has interpreted this portion of Althen as requiring not simply the presentation of a theory, but the presentation of a persuasive theory. M.S.B. by Bast v. Sec'y of Health & Human Servs., 117 Fed. Cl. 104, 123 (2014), appeal dismissed, 579 F. App'x 1001 (Fed. Cir. 2014); Taylor v. Sec'y of Health & Human Servs., 108 Fed. Cl. 807, 819 (2013).

For the reasons previously set forth, Dr. Lokshin has failed to establish the reliability of his theory that T cells have a substantive role in a human being's response to a pneumococcal infection. The theory Dr. Lokshin advanced seems contrary to what science knows about the immune system of human beings. It is not persuasive. Therefore, the petitioners have not met their burden regarding prong 1.

3. Prong 2: Logical Sequence of Cause and Effect

Given that the DePenas have failed to establish prong 1, it follows that they have also failed to establish prong 2. See Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 134 (2011) (discussing the logical connections between prongs 1 and 2). Nevertheless, to demonstrate that the entire record has been reviewed, the following factors have also been considered.

Treating Doctors. In connection with prong 2, the Federal Circuit has instructed special masters to consider carefully the views of treating doctors. Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006). The DePenas conceded that they are "unaware of any statements expressed by treating doctors that indicate the MMR vaccine caused [Rhone] DePena's vulnerability to pneumococcal infection." Pet'rs' Preh'g Br., filed Dec. 15, 2016, at 19. An independent review of the record has also not located any suggestions that treating doctors linked Rhone's receipt of the MMR vaccine to his pneumococcal pneumonia. Thus, this factor does not weigh in the petitioners' favor.

Challenge-Rechallenge. The Federal Circuit defined a rechallenge event as one in which "a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine." Capizzano, 440 F.3d at 1322.

Here, Dr. Lokshin initially indicated that Rhone's case fell into the challenge-rechallenge paradigm. A foundation for this opinion was an assumption that Rhone developed a rash shortly after receiving his first dose of the MMR vaccine. See exhibit 21 (Dr. Lokshin report) at 3; exhibit 8 (Ms. DePena's Detailed Statement) at 1. However, further development of the evidence eliminated this foundation because Rhone's rash developed approximately one year after the MMR vaccine.

On cross-examination, Dr. Lokshin graciously recognized that Rhone did not manifest challenge-rechallenge. Tr. 196. Removing one of the beams of support for Dr. Lokshin's opinion results in a slight weakening of his opinion.

Titer levels after the vaccine and more recently. Before the first hearing, the DePenas submitted the results of testing conducted on October 11, 2010. This testing, which was conducted after Rhone developed pneumonia, showed that his IgG antibody titers were below the level to confer immunity for several strains. Exhibit 7 at 501; see also Tr. 168, 327, 334. Rhone's parents testified that he has

not developed pneumonia after he was hospitalized for pneumonia in 2010. Tr. 34, 59.

From these two facts, Dr. Lokshin drew the inference that the only difference between Rhone in 2010 and Rhone in the ensuing five years was that Rhone received the MMR vaccine in 2010. This exposure to the MMR vaccine, according to Dr. Lokshin's theory, created a vulnerability in Rhone that was not present in other times of his life. Tr. 144-45.

Dr. Romberg's response included an observation that Rhone's current levels were not known. Tr. 333-34. Therefore, between the first hearing and the second hearing, the DePenas had Rhone tested. His antibody levels from 2016 remained below protective levels for several strains. Exhibit 27; see also Tr. 455, 489. To Dr. Lokshin, this finding reinforced his conclusion that antibodies cannot be the only way to prevent infection because if antibodies were the only way to prevent infection, Rhone would have become infected again. Tr. 489-90, 502-03; see also exhibit 30 (Dr. Lokshin's post-hearing expert report) at 7-9; Pet'rs' Posth'g Reply, filed Aug. 26, 2016, at 9.

This reasoning is not persuasive. First, the process from colonization to infection is not understood. Some people develop pneumococcal pneumonia entirely apart from an MMR vaccination. The factor (or factors) that permitted pneumococcal infections in those cases could have been present in Rhone. To isolate the MMR vaccination and consequent decrease in T cells as the reason for Rhone's pneumococcal pneumonia seems to overlook many other potentially contributory factors. For example, the particular bacteria that infected Rhone in 2010 could have been especially virulent and Rhone could have encountered more mild bacteria since then. See Tr. 251; exhibit I (E. Alonso DeVelasco et al., *Streptococcus pneumoniae*: Virulence Factors, Pathogenesis, and Vaccines, 59(4) Microbiological Reviews 591 (1995)); exhibit 23 (Dr. Lokshin's report) at 2. The variability in type of pneumococcal infection, ranging from relatively mild cases of ear infections, to full blown pneumonia, further suggests that process from colonization to infection is complicated.

Second, Dr. Lokshin appears to misunderstand Dr. Romberg's opinion. Dr. Lokshin asserted that "The 'titers' are the antibody levels that, according to Dr. Romberg's theory, is the one and only protection from the pneumococcal infection." Exhibit 31 at 1. Actually, Dr. Romberg listed parts of the innate immune system, such as complement, as contributing to the protection against pneumococcal infection. Exhibit A at 3; exhibit P at 3; Tr. 326-27. These parts of

Rhone's innate immune system could have protected him from further pneumococcal infection in the past six years.[23]

Conclusion

Rhone's pneumococcal pneumonia inflicted a toll on him and his parents. His parents demonstrated their concern for Rhone's well-being during their testimony and have reached the belief that the MMR vaccine caused the pneumonia.

However, the evidence does not rise to a "more likely than not" level. The more persuasive evidence is consistent with a finding that the MMR vaccine did not alter the effectiveness of Rhone's innate immune system or his ability to produce antibodies in response to pneumococcus. Thus, the DePenas have not established that the MMR vaccine contributed to Rhone's pneumococcus infection.

The DePenas are not entitled to compensation. The Clerk's Office is instructed to issue judgment in accord with this decision.

IT IS SO ORDERED.

S/ Christian J. Moran
Christian J. Moran
Special Master

[23] More generally, Dr. Lokshin contended that human beings' response to pneumococcus cannot depend on antibodies because the lag in producing antibodies would permit pneumococcus to flourish and to kill the host. See Tr. 110-11. The innate immune system is a partial response to Dr. Lokshin. The other part of the response is that pneumococcus unfortunately has killed many people over the millennia. See Tr. 156-57, 329. The advent of antibiotics prevents many deaths from pneumococcus. See exhibit 31 (Dr. Lokshin's second post-hearing report) at 2; Tr. 218.